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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,157	04/25/2001	Koichi Nishigaki	P66602US0	4171

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EXAMINER	
SHEINBERG, MONIKA B	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,157	NISHIGAKI ET AL.	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner. (Sequence non-compliant)

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s).~~ *1 sheet* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments filed: 20 March 2003

The cancellation of claims 1-7 and the addition of new claims 8-14 in the amendment filed 20 March 2003 are acknowledged. Claims 8-14 are now pending. Please note that in submission of amended or new claims, a parenthetical expression must indicate each claim's status; for example: *claim 8. (new) A method....*

Applicants' arguments, filed: 20 March 2003, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Sequence Non-Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR § 1.821 through 1.825 because the following pages contain nucleic acid sequences that do not have sequence identifiers. A Sequence Listing and a computer readable format of it must be provided with a statement that the two are identical. The sequences presented in these pages must still be included in the Sequence Listing; and a sequence identifier (SEQ ID NO: X) must be used in the specification. Applicant is reminded that CD-ROM sequence listings are now accepted instead of a paper copy of the sequence listing for the specification. Applicant(s) are given the same response time regarding this failure to comply as that set forth to respond to this office action. A complete response to this office action includes compliance with this sequence rule compliance. Failure to comply may result in abandonment of this application.

Maintained Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 1 with respects to its corresponding new claim 8 is maintained and reiterated from the previous Office action mailed: 08 October 2002. Claim 8 remains unclear due to awkward construction of claim language. The body of the claim lacks clarity in the stepwise manner in which to execute the claimed method as a result of confusing claim language (see lines 10-18):

> (e) comparing the PaSS and /or genome semi-distance(s) which was/were obtained in step d) to PaSS and/or genome semi-distance(s) recorded in a database to identify the organism, wherein the PaSS and/or genome semi-distance(s) recorded in the database is obtained by a method in which steps at to d) are carried out with respect to known organisms under the same conditions as the steps a) to d) carried out on the organism to be identified, and wherein in the electrophoresis by TGGE or DGGE, a standard DNA is co-migrated with the double-stranded DNA fragments as an internal reference for providing a standard point and location of the recorded position of the featuring points is determined in relation to the featuring points of the standard DNA.

The last step (e) appears to describe more than one active step that includes actions misplaced within the body of the claim causing confusing language: 1. comparing recorded data that has not yet been recorded in a database; 2. co-migrating a standard DNA in the electrophoresis performed in step (b); and 3. locating featuring points performed in step (c). For example, in regards to the compared recorded data, the "PaSS and/or genome semi-distance(s) recorded in a database" (line 11) are not recited to be recorded in the said database. The steps of the obtaining data for the database are described within the step of data comparison. Besides steps of obtaining data in the step of comparison, steps of performing actions required at the beginning of the method are included.

In addition, lines 16-18 are confusing in that the featuring points appear to be based upon each other yet not. For example: if the "location of the recorded position of the featuring points is determined in relation to the featuring points of the standard DNA", then it is unclear to what the feature points of the standard DNA originated from then. These steps, as essential elements to

the method practiced, do not follow in a stepwise manner thus making the methodology confusing. The claims must be rewritten to reflect the methodology in a clear stepwise manner. Claims 9-14 are also indefinite due to their dependency from claim 8.

The rejection of claim 1 with respects to its corresponding new claim 8, is maintained and reiterated from the previous Office action mailed: 08 October 2002. Claim 8 remains indefinite for failing to recite a final process step which agrees back with the preamble, "a method for identifying an organism". While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986). For example, claim 8 is drawn to a method for identifying an organism, yet the claim recites a final active step of comparing the recorded data without any method step beyond the comparison as what determines the final identification. In addition, due to the confusion claim language as described above, it is unclear as to what is the determinant of the final identification; for example, the determined 'PaSS' score or the internal reference sample. The claims do not set forth the conditions/state when the method has identified an organism. As such, claims 9-14 are also indefinite due to dependency from claim 8.

The rejection of claim 4 with respects to its corresponding new claim 11 is maintained and reiterated from the previous Office action mailed: 08 October 2002. The term "material" remains unclear due to the lack of clarity in the metes and bounds of the parameters that define the term "material". As stated in the previous action, the "specific material [that] bears the fluorescent marker" must be indicated by the claim. As such, claims 9-14 are also indefinite due to dependency from claim 8.

Applicants have not provided any substantial arguments with regards to the above reiterated rejections, thus no response of persuasiveness is deemed necessary. The amendments to the claims have not clarified the instant claims, thus the rejection has not been overcome.

New Grounds of Rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

- Claims 8, 10, 13 and 14 are rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Nishigaki *et al.* (*Chem. Lett.*, 1991; hereby referred to as Nishigaki-A) in view of Nishigaki *et al.* [*J. Biochem.(Tokyo)*, 1992, p. 144-150; hereby referred to as Nishigaki-B] and Nishigaki *et al.* [*J. Biochem.(Tokyo)*, 1992, p. 151-156; hereby referred to as Nishigaki-C].

The purpose of the instant invention is to identify a characterized piece of genomic DNA (organism) using random PCR and denaturing gradient gel electrophoresis (DGGE) or temperature gradient gel electrophoresis (TGGE). Claim 8 requires the following steps: (a) amplify one or more genomic double-stranded DNA of an organism by random PCR; (b) perform TGGE; (c)-(d) generate specific individual DNA profiles from each TGGE or DGGE electrophoretic pattern.

Nishigaki-A demonstrates a method of random-PCR-based DNA profiling for the purpose of systemic characterization, classification and comparison of genomic DNAs (title and abstract): "DNA profiling introduced here is useful to extract the information which characterizes the whole genome" (p. 1097, 1st paragraph, lines 2-4). The limitations of claim 8, steps (a) and (b), are identical to that of the method taught by Nishigaki-A in Figure 1 while steps (c-e) are demonstrated in a generic fashion (p. 1098 and further described in the 1st column, 2nd – 3rd paragraph). The limitations of steps (a) and (b) are demonstrate by the whole genome of interest being utilized as the template for random PCR, after which TGGE is performed. A general description of steps (c-e) are demonstrated by the staining and viewing of electrophoretic

band patterns which represent transition mobility profiles that are characteristic to each DNA representative of the genome as a whole (p. 1098, 3rd paragraph). The genomic DNA of interest utilized as a template was of three different strains of E.coli (a microorganism, claim 14), (Figure 2, legend). The characteristic patterns that are generated for the profiles encompass the identification of key features [as required by step (c) of claim 8] that correlate each profile to the specific strains of the E.coli and allow for differentiation amongst each strain thus permitting species or homology identification (claim 10 and step (d) of claim 8). Internal references are co-migrated double stranded DNAs (ds DNA) as demonstrated in figure 3 (a-c) labeled A, B, and C. The generated profile is obtained from the band pattern expression by the coordinates of the temperature axis and the mobility axis of TGGE as required by claim 13. Therefore Nishigaki-A demonstrates both exact and general limitations of claims 8, 10, 13 and 14.

Nishigaki-A does not teach the featuring points on the transition mobility profiles as described by the specification on page 17, lines 2-11 (claim 8, step (c)); the specifics of the PaSS or genomic semi-distance [claim 8, step (d)]; nor the incorporation of a database [claim 8 step (e)].

The purpose of Nishigaki-B is the "convenient way" (p. 151, 2nd column, 1st paragraph) of structural analysis of nucleic acids double and single stranded DNAs (ssDNA and dsDNA) in order to apply such an analysis to the identification and characterization changes in sequence content based on mobility transition profiles. Nishigaki-B demonstrates a computerized system, a "precise system" (abstract, line 4), which generates DNA or RNA transition mobility profiles from images of oligonucleotides and polynucleotides run on a "precise" DGGE or a "precise" TGGE. Each oligonucleotide "has its own characteristic normalized mobility profile (NMP) which can be used to identify, characterize and classify the molecules" (abstract, lines 3-4); thus is representative of the internal reference or database reference to which unknown profiles are to be compared to in order to determine similarity score, just as PaSS "pattern similarity score". Such value calculations and comparisons using mobility transition for quantitative analysis of gel images based on extracted key features are demonstrated on page 156 (1st column, 2nd paragraph). Key features or "featuring points" are determined from the mobility profiles based upon "meltings and strand dissociations" (p. 156, 1st column, 2nd paragraph yet the process of selecting featuring points from the images are described in greater detail in the incorporated

reference, Nishigaki *et al.* [*J. Biochem.(Tokyo)*, 1992, p. 151-156; hereby referred to as Nishigaki-C]. Although the demonstrated results in figures 1-8 are specific to oligonucleotides Nishigaki-B states that the "parallelism of denaturing effects between temperature and denaturant concentration has been established for dsDNAs" (2nd column, 2nd paragraph) thus the featuring point extraction and profile analysis are also applied to the dsDNA (see figure 7, p. 155).

As stated above, Nishigaki-B incorporates by reference the teachings of Nishigaki-C for detailing of the methodology for generating the NMPs (p. 152, 1st column, 2nd paragraph), a common reference allowing for a fully quantitative structural analysis with a "relatively simple procedure" (Nishigaki-B, p. 151, 1st column, lines 9-15). Nishigaki-C demonstrates the identification of featuring points from the gels on page 147 (bridging paragraph between columns) and further on page 149 (1st column, 1st-2nd paragraphs) as described within the specification (p. 17, lines 2-11).

The ability to characterize a giant genome as a whole in a method wherein the "mobility transitions are characteristic to each DNA, reflecting its nucleotide sequence"(p. 1098, 3rd paragraph) is clearly demonstrated by Nishigaki-A. It would have been obvious for one of ordinary skill in the art to perform the base method taught by Nishigaki-A and improve on the generic analysis of the mobility transition profiles to include the more detailed and precise methods of mobility transition profile analysis as per the teachings of Nishgaki-B and Nishigaki-C. The latter two references are two parts of one means of structural analysis (see titles of both references below) that follow immediately after each other in the same publication and incorporate each other by reference.

> *Structural Analysis of Nucleic Acids by Precise Denaturing Gradient Gel Electrophoresis: I. Methodology* (pp. 144-150), and
> *II. Applications to the Analysis of Subtle and Drastic Mobility Changes of Oligo- and Polynucleotides* (pp. 151-156).

Thus, it would have been *prima facia* obvious to one of ordinary skill in the art at the time of the invention was made to perform random-PCR-based DNA profiling of Nishigaki-A and further modify the gel analysis to include image analysis, featuring point determination, and database limitations as per the teachings of Nishigaki-B and Nishigaki-C. One of ordinary skill in the art

would have been motivated to do the modifications taught by Nishigaki-B and Nishigaki-C due to the advantages of improved gel analyses means in the computerized "precise system" using "precise" TGGE and DGGE demonstrated. The core goal and method remains the same, DNA profiling for identifying, classifying and characterizing DNA of a whole genome (an organism), as originally presented in Nishigaki-A. As such, claim 8, 10, 13 and 14 are unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C.

- Claim 9 is rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C as applied to claims 8, 10, 13 and 14 above; and further in view of the nucleic acid GenBank sequence entries: accession numbers J02448 and AE000174 (correspond to SEQ ID NOs: 1 and 2 respectively as noted in the previous Office action mailed 08 October 2002).

Nishigaki-A, Nishigaki-B and Nishigaki-C are applied to claims 8, 10, 13 and 14 as described in detail above. Nishigaki-A, Nishigaki-B and Nishigaki-C do not teach SEQ ID NOs: 1 and 2 as required by claim 9. SEQ ID NO: 1 was known at the time the application was filed to be part of the genome of bacteriophage fl isolated from E. coli (GenBank Accession Number J02448, April 1993). It would have been obvious to one of ordinary skill in the art at the time the application was filed to use bacteriophage DNA as a standard based on the prevalence of phage DNA in bacterial genomes and the likelihood that any bacteria to be identified would contain phage DNA. SEQ ID NO: 2 was described in GenBank accession number AE000174, 1997) as a fragment of the genome of Escherichia coli K12. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the application was filed to use a portion of the genome of E. coli as a standard because of its status as one of the most extensively studied bacteria and its ready availability in a research setting. Furthermore, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the application was filed to use a DNA standard of phage (SEQ ID NO: 1) or bacterial (SEQ ID NO: 2) origin with known length, sequence, and characteristics as a reference for measuring the band patterns generated by a sample to be assayed rather than isolating, purifying, and characterizing a previously unknown fragment of DNA for the same purpose. As such, claim 9 is unpatentable over Nishigaki-A in

view of Nishigaki-B and Nishigaki-C as applied to claim 8, 10, 13 and 14; and further in view of the nucleic acid GenBank sequence entries: accession numbers J02448 and AE000174.

- Claims 11 and 12 are rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C as applied to claims 8, 10, 13 and 14 above; and further in view of Pena *et al.* (*PNAS*, 1994).

Nishigaki-A, Nishigaki-B and Nishigaki-C are applied to claims 8, 10, 13 and 14 as described in detail above. Nishigaki-A, Nishigaki-B and Nishigaki-C do not teach utilizing a fluorescently labeled primer or nucleotide in PCR for use in image processing of the electrophoretic bands as required by claims 11 and 12. Pena *et al.* utilizes a fluorescent primer (claim 12) in a method of PCR for greater resolution of electrophoretic band patterns (claim 11) that are used for generating unique "gene signatures" (p.1948, 2nd column, 1st-2nd paragraph). Thus it would have been *prima facia* obvious for one of ordinary skill in the art at the time of the invention was made to perform random-PCR-based DNA profiling of Nishigaki-A as modified by Nishigaki-B and Nishigaki-C; and further modify the PCR to include a fluorescent primer for improved image processing techniques as per the teachings of Pena *et al.* for reasons that the "resolution is much superior" (p.1948, 2nd column, 2nd paragraph, line 9) over silver staining. [Nishigaki-A uses silver staining, see Figure 1-(3)]. One of ordinary skill in the art would have been motivated to perform the modifications as per Pena *et al.* because Pena *et al.* extended their own technique to include fluorescence in their image processing for "increasing throughput and accuracy"(p.1948, 2nd column, 2nd paragraph, lines 1-2) in generating "gene signatures". As such, claims 11 and 12 are unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C as applied to claim 8, 10, 13 and 14; and further in view of Pena *et al.*

Conclusion

- Claims 8-14 are rejected under 35 U.S.C. 112, second paragraph. This rejection is maintained and reiterated from the previous office action with respect to the canceled claims 1-7.

- Claims 8, 10, 13 and 14 are rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C.
- Claim 9 is rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C as applied to claims 8, 10, 13 and 14 above; and further in view of the nucleic acid GenBank sequence entries: accession numbers J02448 and AE000174.
- Claims 11 and 12 are rejected as necessitated by amendment, under 35 U.S.C. 103(a) as being unpatentable over Nishigaki-A in view of Nishigaki-B and Nishigaki-C as applied to claims 8, 10, 13 and 14 above; and further in view of Pena *et al.*

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can

normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the primary examiner in charge of the prosecution of this case, Jehanne Souya, can be reached at 703-308-6565. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

June 30, 2003

Monika B. Sheinberg
Art Unit 1634

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